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Trends of human brucellosis in Italy, 1998–2010

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SUMMARY

We describe the epidemiological trends and spatial distribution of human brucellosis in Italy over 13 years (1998–2010). In the study period 8483 cases were notified in Italy, with a relevant decrease (−89%) from 1998 to 2010. Most cases were notified in southern Italy (Campania, Apulia, Calabria, Sicily). In these regions we observed relevant differences in the risk of brucellosis at province level. Cases were distributed with a seasonal pattern, male patients represented 60% of the cases and no significant differences were observed between age groups. We modelled the underreporting rate that ranged between 2 and 21 (average 12·5). According to our estimates the true number of cases would have ranged from 41 821 to 155 324 providing a far more severe picture of human brucellosis in Italy than the one provided by the surveillance system.

Key words: Brucellosis, epidemiology, public health, zoonoses.

INTRODUCTION

Brucellosis is a worldwide zoonotic disease caused by *Brucella* spp. From a public health point of view, the most relevant species are *B. melitensis, B. abortus* and *B. suis*. The first species infects mainly sheep and goats, but can also infect bovines, *B. abortus* is mainly transmitted from bovines and buffalos, while pigs are the main reservoir for *B. suis* [1].

Human infection is acquired by direct contact with body fluids and tissues of infected animals or, more often, through the consumption of raw animal products, such as unpasteurized milk or cheese, whereas human-to-human transmission is rare [2]. About 500 000 cases/year of human brucellosis are reported worldwide, but the estimates of the World Health Organization (WHO) suggest that, due to underreporting, the real incidence is 10–25 times higher [3].

In Europe, brucellosis is declining, according to data from the European Food Safety Authority (EFSA) the number of cases decreased from 735 in 2008 to 352 in 2011 (EFSA, 2013). The disease affects mostly the Mediterranean countries. From 2008 to 2011 Greece, Italy, Portugal and Spain accounted for 50–80% of all the European reported cases, respectively, with *B. melitensis* and *B. abortus* being

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the predominant causative agents [4]. As the risk of human brucellosis is closely related to infection rates in ruminants, the implementation of eradication programmes in these animals, where achieved, may markedly reduce the incidence of the disease in humans [5–7].

In Italy, brucellosis has been a notifiable disease since 1934. It has long been an endemic disease, reaching its highest incidence (>20 cases/100 000 inhabitants) in the years following the Second World War [8]. Intervention measures aimed at eradicating the disease in ruminants started in the late 1960s. As a consequence of vaccination and culling of infected cattle, sheep and goats (Decree of the Italian Ministry of Health no. 651, 27 August 1994; Decree of the Italian Ministry of Health no. 453, 2 July 1992), the incidence of human brucellosis steadily declined [8, 9].

Since the end of the 1990s, a progressive increase in the number of Italian provinces free from animal brucellosis has been observed, in particular the northern regions. However, in the southern regions the disease is still circulating in cattle, sheep and goats [10], particularly in Campania, Apulia, Calabria and Sicily, where 22% of cattle farms, and 29% and 34% of sheep and goat herds, respectively, are located [11]. In these four regions, a specific eradication programme has been enforced since 2006 (Order of the Italian Ministry of Health, 14 November 2006). As a result, the proportion of positive herds decreased considerably, but the number of newly infected herds (annual incidence) maintained comparable values or even increased as observed in Sicily and Calabria [10, 12]. The decreasing trend of human brucellosis observed in Italy since the late 1960s was confirmed by a recent study that also showed a geographical clustering of cases in the southern regions, with evidence for predominant foodborne origin of human cases [5].

In order to update the epidemiological trends of human brucellosis in Italy, we analysed surveillance data from 1998 to 2010. Moreover, we described the geographical distribution and estimated the under-reporting rates of the disease, providing background epidemiological information necessary for targeting public health interventions aimed at improving prevention and control of the disease.

MATERIALS AND METHODS

Data sources

Data on brucellosis cases which occurred in Italy were collected from two different sources: the mandatory National Surveillance System of Infectious Diseases (SIMI) [13] and the Hospital Discharge Records (SDO) [14].

In Italy brucellosis is a notifiable disease and, according to SIMI procedures provided by Italian legislation (Decree of the Italian Ministry of Health, 15 December 1990), a case of brucellosis must be notified by the physician to the local health unit within 48 h. SIMI notification forms report personal details of the case and if the case is hospitalized or not. For the purpose of this study, all brucellosis cases notified to SIMI between 1998 and 2010 were collected by age, gender and province of residence.

SDOs were officially adopted in Italy mainly for administrative purposes to define the cost of each hospitalization and the reimbursement rate from the Italian National Health System. SDOs are completed for every hospitalized patient. In the SDO, up to six different concomitant diseases can be registered as cause of hospitalization, and are coded according to the International Classification of Diseases (ICD-9-CM for the considered period). In addition, information regarding the procedures and kind of care provided during the hospitalization are collected. All public and private hospitals send the SDOs to the regional competent health authority and then to the Ministry of Health [14]. Hospitalizations for brucellosis between 2001 and 2010 were selected by code (ICD-9-CM from 023 to 023·9), searching all six levels of diagnosis. In the analysis, for patients hospitalized more than once, only the first hospital admission was counted, but the total number of days of hospitalization due to brucellosis was calculated considering also the repeated hospital admissions.

Mortality data for brucellosis were obtained for the years 2000–2008 from the Italian National Institute of Statistics (ISTAT) [15]. Official mortality data in Italy are not available for the years 2004 and 2005. Mortality was also extracted from the SDOs with the outcome 'death' for hospitalized cases.

Statistical analysis

The annual total number of cases and the annual incidence rates per age group and gender were calculated at the national level for the entire study period (1998–2010). The significance of incidence temporal trends was tested using the Cuzick's test for trends. Seasonal distribution of cases was assessed by calculating the average mean number of cases per month and the mean monthly incidence rate (1998–2010).

Table 1. *Parameters used to estimate the real number of brucellosis cases occurred in Italy (1998–2010)*

Notation	Description	Estimation
i	Subscript for year	–
j	Subscript for region	–
S_i	Number of SDOs reporting ordinary hospitalized cases in year i	Data
$Y_{\mathrm{tot},i}$	Total number of SIMI notifications in year i	Data
$y_{h,i}$	Number of SIMI notification of cases who were hospitalized in year i	Data
$y_{nh,i}$	Number of SIMI notification of cases who were not hospitalized in year i	Data
Ir_{ij}	Incidence rate/100 000 inhabitants in year i and region j	Data
$Py_{nh,i}$	Probability of a SIMI notification to be a non-hospitalized case in year i	$\sim\mathrm{Beta}(y_{nh,i};\ y_{h,i})$
$Py_{h,i}$	Probability of a SIMI notification of an hospitalized case to be also reported as a SDO in year i	$\sim\mathrm{Beta}(y_{h,i};\ S_i - y_{h,i})$
$E_{nh,i}$	Estimated number of cases who were not hospitalized in year i	$\sim\mathrm{Bin}(Y_{\mathrm{tot},i};\ Py_{nh,i})/Py_{h,i}$
$E_{\mathrm{tot},i}$	Estimated total number of cases in year i	$S_i + E_{nh,i}$
$\mathrm{UR}_{\min}$	Minimum under-reporting factor	$\Sigma_i(E_{\mathrm{tot},i}/Y_{\mathrm{tot},i})/13$
$I_{\max,i}$	Estimated highest incidence in the four regions* in year i	$\sim\mathrm{Lognormal}(\mathrm{Ir}_{ij}\ \max;\ 1)$
$I_{\min,i}$	Estimated lowest incidence in the four regions* in year i	$\sim\mathrm{Lognormal}(\mathrm{Ir}_{ij}\ \min;\ 1)$
$\mathrm{UR}_{\max}$	Maximum under-reporting factor	$\Sigma_i(I_{\max,i}/I_{\min,i})/13$

SDO, Hospital Discharge Records; SIMI, National Surveillance System of Infectious Diseases.
* Campania, Apulia, Calabria, Sicily.

Incidence rates were calculated using as denominator the 2005 Italian population data by gender, age and province of residence [15].

Spatial and temporal variations in the distribution of cases were analysed by dividing the study period (1998–2010) into four sub-periods (1998–2000 2001–2003, 2004–2006, 2007–2010) and calculating the average incidence in each sub-period at province level (NUTS3).

For those regions previously identified at high risk for brucellosis (Campania, Apulia, Calabria, Sicily) [5], a multilevel mixed-effects Poisson regression model for the calculation of incidence rate ratios (IRRs) was used to estimate the difference in the risk of brucellosis at the province level. As outcome variable, the number of cases by province was used, while the predictors were province and year of observation. The latter predictor was included to account for the inter-annual trend in the number of cases. The resident provincial population was included as offset in the model. To account for the lack of independence of observations made over time within the same regions, a region-level random effect was included in the model.

To estimate the real number of brucellosis cases that occurred in Italy during the study period, under-reporting rates were estimated as proposed by Gkogka *et al.* [16]. The estimate is given by $\Sigma_i Y_{\mathrm{tot},i} \times \delta$, where $Y_{\mathrm{tot},i}$ is the total number of SIMI notifications in year i, and δ is the underreporting factor obtained by a PERT distribution whose lower and upper bounds, denoted as $\mathrm{UR}_{\min}$ and $\mathrm{UR}_{\max}$, respectively, are defined in Table 1. The most likely value of the PERT distribution was set in the middle of the range between $\mathrm{UR}_{\min}$ and $\mathrm{UR}_{\max}$ to give equal weight to the extremes.

As reported in Table 1, the $\mathrm{UR}_{\min}$, which corresponds to the lower bound of the PERT distribution, was calculated considering the two sources of the data on hospitalized cases: SIMI and SDO. Briefly, SDOs have been matched with the hospitalized cases derived from SIMI notifications. Assuming that the SDOs represent the true number of hospitalized cases, and the proportion of hospitalizations provided by SIMI over the total number of notified cases is correct, the proportion between SDO and SIMI hospitalizations provides the multiplier for the number of SIMI notifications to obtain the expected number of notified cases, according to the equation:

$$\frac{\begin{array}{c}\text{no. of hospitalizations}\\ \text{from SIMI}\end{array}}{\begin{array}{c}\text{no. of notifications}\\ \text{from SIMI}\end{array}} = \frac{\text{no. of SDOs}}{\begin{array}{c}\text{expected no. of}\\ \text{notified cases}\end{array}}.$$

The rate of the calculated and observed number of brucellosis cases over the 13-year study period gave the $\mathrm{UR}_{\min}$ value.

The $\mathrm{UR}_{\max}$ (upper bound of the PERT distribution) was the mean difference in brucellosis incidence in the regions of Campania, Apulia, Calabria

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and Sicily during the 13-year study period. Assuming that these four regions had the same risk for brucellosis, differences in the reported incidence were therefore attributed totally to underreporting as done elsewhere [16]. Uncertainty was introduced in the estimates by specifying appropriate prior distributions as reported in Table 1.

Statistical analysis was performed with Stata v. 11.2 (StataCorp., USA) and Microsoft Excel 2010 (Microsoft Corp., USA). Statistical significance was set at 0.05. All the maps were constructed using Quantum GIS [Quantum GIS Geographic Information System, Open Source Geospatial Foundation Project (http://qgis.osgeo.org)] [17]. All simulations were performed using @RISK 5.7 (Palisade Corp., USA) and for each simulation 100 000 iterations were performed by applying the Latin hypercube technique using a fixed seed value of 1.

RESULTS

All analyses were performed using both data sources (SIMI and SDO), but the results are presented considering the SIMI notifications only; SDOs are presented only in case of significant differences between the two data sources.

In Italy, from 1998 to 2010, 8483 human cases of brucellosis were notified to SIMI. In the 10-year period for which SDO data were available (2001–2010), 6946 hospitalized cases for brucellosis, of which 5462 ordinary (79%) and 1484 day hospital discharges (21%), were recorded. Between 2001 and 2010, SDOs and SIMI notifications only partly overlapped and the average ratio between SDOs and SIMI notifications was 1·2. As not all hospital admissions are usually notified to SIMI, differences in the number of cases between the two sources may occur.

During the 13-year period (1998–2010), the number of notified cases decreased by 89% (Cuzick's test, $P<0{\cdot}005$). This decrease was constant from 1998 to 2004, but in 2005 an increase in incidence was observed. The incidence slightly decreased again from 2006 to 2010. Campania, Apulia, Calabria and Sicily notified 89% of the cases that occurred in Italy from 1998 to 2010. Also in these regions the annual number of reported cases has declined significantly over time (Cuzick's test, $P<0{\cdot}005$). The incidence by province in the four sub-periods (Fig. 1) showed the decreasing temporal trend in the whole country, with a decrease of incidence in almost all provinces and an increase of provinces with no human cases reported. Provinces in the regions of Campania, Apulia, Calabria and Sicily were among those with the highest incidence in all sub-periods.

Cases were distributed with a seasonal pattern, 44% occurring in spring (April–June) with a peak in May (144 cases reported on average) (Fig. 2). This seasonal pattern was consistent in each year of the study period (data not shown).

Male patients numbered 5092 (out of 8376 cases for which gender information was available) in the whole period and represented about 60% of the reported cases.

The incidence of brucellosis by age group showed some differences when the analysis was performed considering the whole country, or only the four regions, with the highest incidence. In the whole country, the highest incidence was observed in the 20–29 years age group, with a mean annual incidence of 1·4 cases/100 000 inhabitants, while the age group with the lowest incidence was $\geqslant 80$ years (mean annual incidence 0·4 cases/100 000). The other age groups showed an incidence ranging between 0·8 and 1·3 cases/100 000.

When only cases occurring in Campania, Apulia, Calabria and Sicily were considered, the highest incidence was in the 50–59 years age group (mean annual incidence 4·8 cases/100 000), while the lowest incidence was in the 0–9 years age group (1·9 cases/100 000). The incidence in the other age groups ranged between 3·2 and 4·5 cases/100 000.

Overall, 72% of cases notified to SIMI were hospitalized (the SIMI notification form also reports whether the case was hospitalized or not). From 2001 to 2010 according to the SDO, a total of 75 930 days of hospitalization were due to brucellosis. The median duration of a hospitalization was 6 days (interquartile range 8 days).

From 2001 to 2010, according to the SDOs, a total of 19 deaths were recorded in hospitalized cases with brucellosis, while ISTAT reported 11 deaths attributed to brucellosis during the 7 years between 2000 and 2008 for which mortality data were available.

Results of the multilevel mixed-effects Poisson regression model showed that in Campania, Apulia, Calabria and Sicily there were differences in the risk of brucellosis (expressed as IRR) at the province level (Fig. 3). An IRR >15 was found in 4/9 provinces of Sicily and in one province of Calabria. The model also confirmed the significantly decreasing trend of

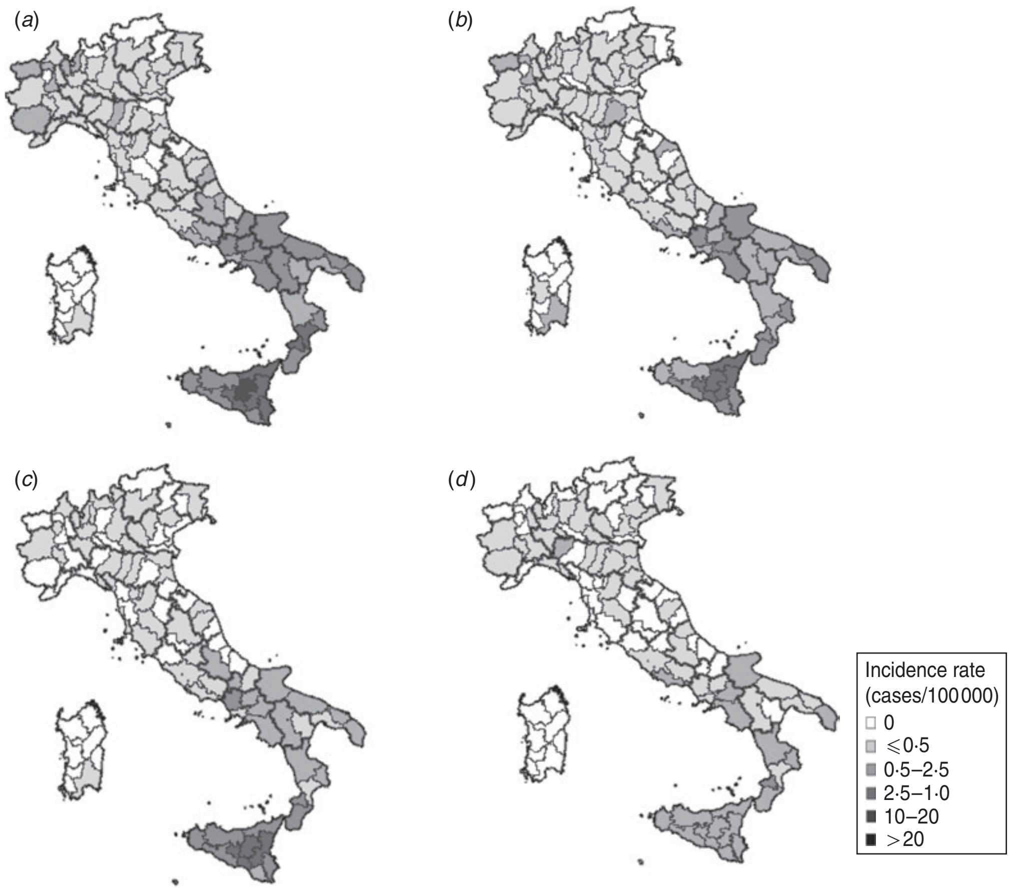

Fig. 1. Average incidence rate (no. of cases/100 000 inhabitants) of brucellosis in the Italian provinces during the four sub-periods from 1998 to 2010. (*a*) 1998–200, (*b*) 2001–2003, (*c*) 2004–2006, (*d*) 2007–2010. Data from the National Surveillance System of Infectious Diseases (SIMI).

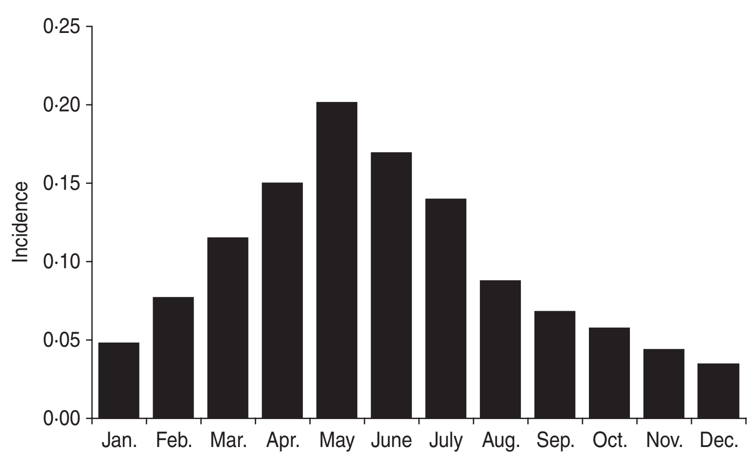

Fig. 2. Average monthly distribution of the incidence (no. of cases per 100 000/month) of brucellosis in Italy from 1998 to 2010. Data from the National Surveillance System of Infectious Diseases (SIMI).

the risk of brucellosis over years. Taking the year 1998 as reference (IRR 1), the IRR decreased reaching an IRR of 0·1 in 2010. Only between 2004 and 2005 did the IRR increase, from 0·3 to 0·5.

The mean estimate of the UR_{min} was 2·1 while the mean estimate of the UR_{max} was 21·1. The average estimate between these two values was 11·6. These parameters were used for specifying the PERT

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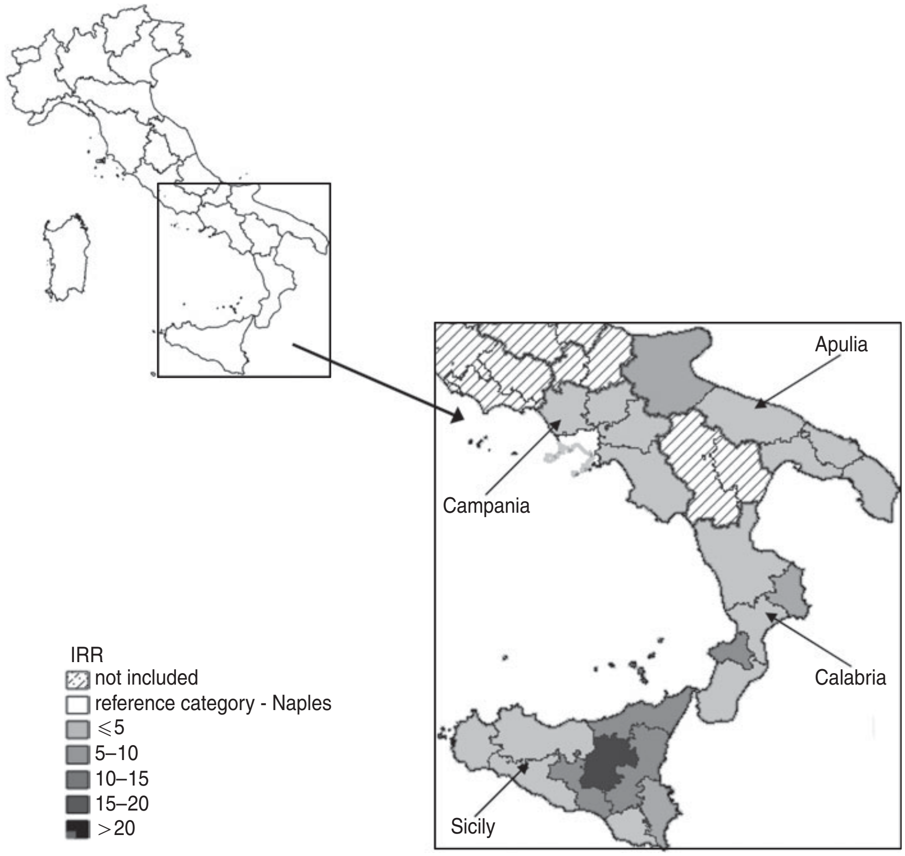

Fig. 3. Incidence rate ratio (IRR) for human brucellosis in the provinces of Campania, Apulia, Calabria and Sicily. Data from the National Surveillance System of Infectious Diseases (SIMI).

distribution that estimated the underreporting rate (δ). The simulation provided an estimated underreporting rate ranging from 5 to 18. According to this estimate, for the whole study period the number of cases would have been 98 572 (range 41 821–155 324) instead of the 8483 notified.

DISCUSSION

This study confirms the decreasing temporal trend of human brucellosis observed in Italy [5]. Nevertheless, differences in the distribution of the disease across the country were observed. Most of the cases (89%) were notified in the southern regions of Campania, Apulia, Calabria and Sicily. In particular, the provinces at the highest risk were in Sicily and Calabria.

As observed in other countries [18], in Italy the incidence of brucellosis increased from January to May and decreased from June to December. This seasonal pattern is related to the availability of dairy products at high risk for contamination, such as unpasteurized milk, and fresh cheese, that are produced mainly in the spring, when dairy sheep and goats are in the lactation period [5].

We observed a rather homogeneous distribution of cases between the different age groups. The difference in incidence by age observed between Italy as a whole and the regions of Campania, Apulia, Calabria and Sicily may be explained by the fact that people aged <30 years represent a higher proportion of the whole population in the southern regions compared to the northern regions [15].

In agreement with the literature [18, 19], we found a higher incidence in males compared to females. This is plausible considering that men may be professionally more exposed than women [18], as men are more often employed as farm workers, shepherds, slaughterhouse workers and veterinarians, professions considered as high risk for brucellosis [20].

Given our results, we can consider two distinct epidemiological patterns of brucellosis in Italy, both of which are strictly related to the situation of the disease in the main animal reservoirs. In the northern regions, where the disease in animals is under control and many provinces reached the 'officially free from brucellosis' status, human cases are sporadic and not related to local epidemiological factors, but often due to foodborne exposure occurring abroad [21]. On the other hand, in southern regions where brucellosis is circulating in animals at relatively high prevalence (in Sicily in 2009, 7% of bovine herds and 13% of ovicaprine herds were infected [10]) the epidemiology is similar to other areas where the disease is endemic, with lack of clustering of the cases in a particular age group, and a predominance of male cases as a consequence of the above-mentioned occupational exposure [18]. The endemicity of brucellosis in southern regions is also indicated by a previous study showing a seroprevalence of 3% for *Brucella* spp. in the general human population [22]. The areas at higher risk (high IRR) are characterized by sheep and goat farming and production of milk and dairy products. In most of these farms, milking is still done by hand, and the largest share of milk is used to produce typical cheeses for the local market or directly sold by farmers to the consumers. In the areas where the disease is endemic, both foodborne and occupational exposure occur, but the main route of human infection seems to be through food [5, 23].

The figures for the impact of brucellosis in Italy as derived from the estimates of underreporting are far more severe than those provided by the surveillance data. It is known that passive surveillance of infectious diseases, including brucellosis, suffers from underreporting, with different rates depending on the severity of the disease and the capacity of the surveillance system. In Italy, the higher underreporting rate in southern regions compared to the northern ones has been demonstrated for different diseases and could be related to differences in the performance of healthcare facilities [24]. Regarding brucellosis, it is known that not all cases are reported and that estimates of underreporting are affected by considerable uncertainty. In our study, the estimate of UR_{min} was 2. As brucellosis is characterized by long-lasting clinical signs, a low underreporting rate would, in theory, be expected [16]. On the other hand, the UR_{max} was as high as 21. Such a high rate is in line with a study performed in Greece, a country with endemic brucellosis, and the estimates of the WHO [3, 16].

We found a case-fatality rate of 0·2%. This is in agreement with other studies that estimated the fatality rate due to brucellosis to be <2%, mostly as a consequence of endocarditis or central nervous system involvements [16]. We also observed that the majority (79%) of the cases were hospitalized, with a median hospitalization of 6 days. This finding is particularly relevant because it indicates that the magnitude of the impact of brucellosis on the national health system is still significant and that eradication policies in animals need to be continued in order to reduce the disease burden in humans [25].

This study has some limitations related to the quality of the data used for the analyses and the assumptions made. We did not consider variables like the profession, social status or other relevant information that can provide insight for the risk factors and the routes of exposure to brucellosis because, for most of the cases, only data on residence, age and gender were available. Moreover, the geographical representations were made taking into account the residence of the case and not the place of exposure, which may often differ in those cases notified in northern regions [21]. Moreover, the estimate of the underreporting rate with a capture–recapture analysis, often used to adjust for the extent of incomplete ascertainment, with the two data sources available (SIMI and SDO) was not possible because we could not link the cases from the two sources since data are anonymous and not coded unequivocally [26].

In conclusion, we have provided an update of the epidemiology of brucellosis in Italy, confirming the decreasing trend of the disease in humans, with some exceptions in areas at high risk, mainly located in Sicily and Calabria. We also highlighted the public health impact that brucellosis still has in Italy and provided estimates of the underreporting rate, basic information for public health managers to consider in defining intervention strategies and control measures for the disease.

DECLARATION OF INTEREST

None.

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